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Interactions of Slow Electrons with Biomolecules

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Abstract. We report on results of computational studies of the interaction of slow electrons with the purine and pyrimidine bases of DNA, as well as with their associated nucleosides and nucleotides. The calculations focus on characterisation of the π^* resonances associated with the bases and also provide general information on the scattering of slow electrons by these targets. High-level studies of the π^* resonances in pyrazine, a close analogue of the pyrimidine bases, indicate that the higher-energy π^* resonances in these bases may in fact contain large admixtures of core-excited character built on low-lying triplet states. Decay into such triplet states may provide a mechanism for damage to DNA.

1. Introduction

The seminal observations of Sanche and collaborators demonstrating that slow electrons induce single- and double-strand breaks in DNA [1, 2, 3, 4] have stimulated significant interest in studies of the interactions of low-energy electrons with the constituents of DNA and RNA [5]. Because damage is observed at sub-ionisation and even sub-excitation energies, and because the rate of damage exhibits peaks as a function of the incident electron's energy, processes involving resonances in the electronically elastic channel are implicated, particularly resonance-enhanced dissociative attachment (DA). Elucidation of where and how electrons are captured to form temporary anions and understanding how these anionic states promote disruption of the DNA structure are thus crucial to a full understanding of the underlying mechanisms by which slow electrons damage DNA. Dissociative attachment to the nucleobases [6, 7, 8, 9, 10] has been the focus of numerous experimental studies, which have not only demonstrated that resonant dissociative attachment does indeed occur in these bases but have also provided the mechanistic insight that gas-phase DA may be driven largely by vibrational Feshbach resonances built on dipole-bound temporary anions rather than by shape resonances involving trapping of the electron in an empty valence orbital. However, there have been comparatively few studies of low-energy electron scattering by the nucleobases, nucleosides, and nucleotides. To our knowledge, the only measurement of elastic scattering cross sections is that of Abouaf and Dunet [11] for uracil, and their result is relative and at the single angle of 90°. However, the electron-transmission studies of the nucleobases by Scheer *et al.* [8] and Aflatooni *et al.* [12] have revealed the energies and widths of resonances in the low-energy total scattering cross section, which have been assigned as valence shape resonances associated with the vacant π^* orbitals. The few calculations of the electron collision cross sections have generally employed one-electron, potential scattering models [13, 14, 15, 16] and have yielded low-energy elastic cross sections whose resonance positions disagree with the measured positions [8, 12, 14, 16, 17]. High-level computational studies that characterise the resonance structures in electron collisions

with subunits of DNA could well provide valuable insight into the mechanism by which slow electrons damage DNA.

In this article we report on some recent results of our first-principles calculations of low-energy electron-collisions with biological molecules, including DNA and RNA nucleobases, nucleosides, nucleotides, and backbone constituents [18, 19, 20, 21]. An emphasis of these studies has been the characterisation of low-energy π^* resonances [8, 12] that may promote dissociative attachment. Our studies indicate that some low-lying resonances typically thought of as elastic shape resonances in fact contain large admixtures of core-excited character, thus representing not only an interesting case of resonant channel coupling but also a possible mechanism for promoting dissociative excitation.

2. Some computational aspects

Our work employs the Schwinger multichannel (SMC) method. Although the SMC method [22, 23] and its implementation [24, 25] have been described elsewhere, it will be helpful to briefly review a few features of the method underlying our studies. The SMC method is an all-electron variational formulation of electron collisions. It is applicable to arbitrary polyatomic molecules and treats inelastic as well as elastic scattering. A key point to note in the SMC variational expression for the scattering amplitude is the occurrence of a Green's function term, whose evaluation becomes the principal computational task, and another is that all of the matrix elements required are indeed independent of the asymptotic form of the wave functions [22, 23]. This latter fact justifies the use of square-integrable basis sets, such as Cartesian Gaussians commonly used in quantum-chemical calculations, for expressing the trial functions in numerical applications of the variational principle. However, even when Cartesian Gaussians are chosen as the basic one-electron functions in the $(N+1)$-electron Slater determinants employed in the expansion of the trial scattering wavefunction, two important differences remain between the SMC method and bound-state problems. First, matrix elements involving both Gaussians and plane waves are required. However, these integrals can be computed by techniques analogous to those used for Gaussians alone. Second, a class of matrix elements that include a Green's function term arises, and these are more difficult to evaluate than the usual one- and two-electron operators. With a spectral representation of the Green's function, this term can be evaluated by a quadrature which, however, requires mixed integrals involving both Gaussians and plane waves for a large range of wave vectors $\mathbf{k}$.

Both the number of elementary integrals and the amount of work required to manipulate them increase rapidly with size of the one-electron basis set, and therefore with the size of the molecule. For modest-sized polyatomics containing five to ten heavy atoms, 10^{10} to 10^{12} integrals might be required, and the number of floating-point operations involved may range from 10^{13} to 10^{15} or more. Fortunately, both evaluating and manipulating the elementary integrals over Gaussians and plane waves are procedures amenable to parallelisation. By formulating the SMC method for massively parallel computers [25], we have been able to achieve sustained performance in the hundreds of gigaflops, making practical studies of electron collisions with polyatomic molecules as large as buckminsterfullerene, C_{60} [26], and the DNA nucleotide 2′-deoxyadenosine 5′-monophosphate [19].

3. Results and Discussion

In this section we will review the results of calculations of elastic electron scattering by the purine base adenine, its nucleoside 2′-deoxyadenosine (dA), and its nucleotide 2′-deoxyadenosine 5′-monophosphate (dAMP) to illustrate some aspects of the findings and strategy of our studies of the interaction of slow electrons with biomolecules. The structures of these molecules are shown in Fig. 1, and details of the calculations can be found in [18].

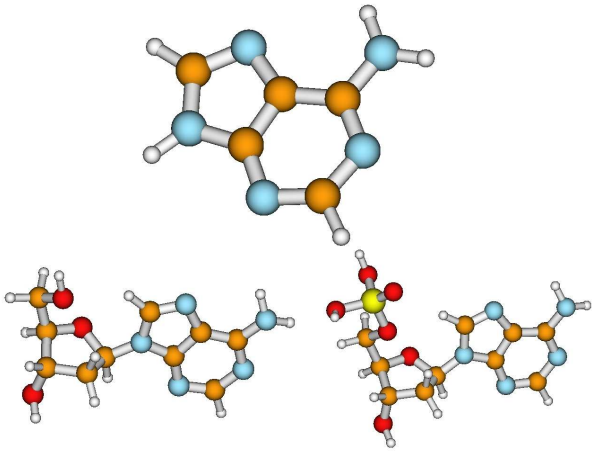

Figure 1. Molecular structures of adenine (top), 2′-deoxyadenosine (bottom left), and 2′-deoxyadenosine 5′-monophosphate (bottom right). Oxygen atoms are red (dark) spheres, carbon atoms brown (medium), and nitrogen atoms blue (light); hydrogen atoms are small white spheres; phosphorus is the yellow (light) sphere surrounded by four oxygens.

Adenine is a nearly planar molecule, with the largest departure from plane geometry involving the hydrogen atoms on the amine group. Imposing a planar geometry on the molecule facilitates the computations and their analysis by allowing us to separate the orbitals and electronic states into representations of the C_s group; in particular, the π^* resonances fall into the $^2A''$ representation and can be more readily distinguished from the large $^2A'$ background. However, distorting the molecular geometry may shift resonance positions, as we recently found, for example, in tetrahydrofuran [21]. Accordingly, though we carried out most of our calculations in the planar geometry, we compared static–exchange (no polarisation) cross sections at the C_s and undistorted (C_1) geometries for the purine base guanine and determined that the π^* resonances are shifted up by about 0.2 eV in the planar configuration. Furthermore, adenine, dA, and dAMP all possess dipole moments, and long-range scattering of electrons by the dipole potential leads to large forward scattering that can be difficult for methods that rely on finite basis sets and/or partial-wave expansions to capture. Though there are procedures for correcting the calculated cross sections to account for such long-range scattering, we have neglected such corrections because they are not expected to significantly affect the π^* resonance energies of interest here.

Fig. 2 shows our calculated A″ component of the low-energy integral cross section for elastic scattering of electrons by adenine at the static–exchange (SE) level (no polarisation). This component of the cross section contains the π^* shape resonances, which appear as three narrow peaks between 3 and 5 eV and a fourth peak just above 10 eV. Convergence of the positions of these resonances was checked by carrying out calculations with several large basis sets [18], and the cross sections in Fig. 2 were obtained with the largest and spatially most extensive of these, which actually begins to capture the enhancement of the cross section by the long-range interaction between the electron and the dipole moment of adenine. Because static–exchange calculations neglect polarisation effects which are important at low energies, the three lowest resonances in Fig. 2 lie well above the experimental positions of 0.54, 1.36, and 2.17 eV [12]. Static-exchange calculations, in fact, provide upper bounds to resonance positions because the omitted polarisation interaction is net attractive.

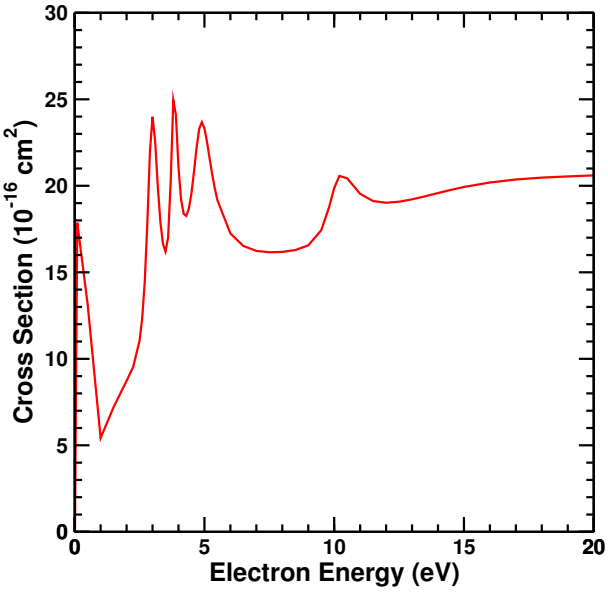

Figure 2. A'' symmetry component of the integral elastic cross section for electron scattering by adenine as computed in the static–exchange approximation. The peaks from 3–5 eV and near 10 eV are due to π^* shape resonances, while the rise below 1 eV is due to nonresonant scattering by the dipolar potential.

To include polarisation effects in the SMC method, closed-channel terms must be added to the $(N+1)$-particle variational space [23, 24]. To form these closed-channel terms, the virtual orbitals are first transformed into modified virtual orbitals that are constructed by diagonalising a cationic Fock operator within the virtual-orbital space (thus preserving orthogonality to the occupied orbitals) [27]. The lowest-energy modified virtual orbitals are localized near the molecule and valence-like, and thus well suited to representing polarisation of the target charge density. In the present application to the $^2A''$ component of the cross section in adenine [18], the three lowest-energy a'' modified virtual orbitals were coupled with all singlet coupled, singly excited N-electron configurations that could be formed by exciting from an occupied valence orbital into an empty orbital of the same symmetry. This procedure attempts to describe the relaxation of the target molecule's charge density in the presence of an electron temporarily trapped in a π^* orbital. The resulting variational space contained about 10,000 configuration state functions.

Our calculated $^2A''$ component of the cross section for adenine including polarisation is shown in Fig. 3. We show results only up to 5 eV because of pseudoresonances at higher energy which make it difficult to determine the actual location of the fourth π^* resonance. Polarisation shifts the first three resonances downward to about 1.1, 1.8, and 4.1 eV, compared to the experimental positions of 0.54, 1.36, and 2.17 eV [12]. For comparison, the calculations of Tonzani and Greene [16] yield π^* resonance energies of 2.4, 3.2, 4.4, and 9 eV in adenine, which are higher than the energies we obtain, particularly for the first two resonances. Tonzani and Greene [16] employed a one-electron scattering model in which the exchange and polarisation potentials are approximated by local potentials. Both approximations may introduce errors, but because the same method places the $^2\Pi_u$ shape resonance of CO_2 about 2 eV higher in the SE approximation than do accurate all-electron SE calculations [28], the local approximation to exchange may well be the main source of error in their calculated resonance energies.

The calculated resonance positions in Fig. 3 are about half an eV too high for the lowest

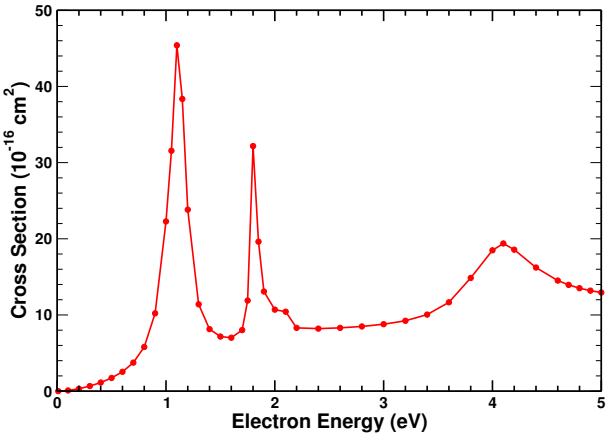

Figure 3. A'' component of the integral elastic cross section for electron scattering by adenine as computed in the static–exchange plus polarisation approximation. The three prominent peaks are due to π^* resonances.

two resonances and about 2 eV for the third. We have observed this pattern consistently in elastic calculations on the purine and pyrimidine nucleobases of DNA and RNA [18, 19, 20]: The calculated positions of the two lowest and narrowest resonances agree fairly well with experiment, but our results for the third and broadest resonance are too high. While these discrepancies may in part arise from limitations of our treatment of polarisation, we would have expected such limitations to be less important for the third resonance than for the two lower-energy and narrower resonances. In [18] we surmised that the larger discrepancy for the third resonance may arise from our restriction of the closed-channel space exclusively to configurations describing relaxation of the ground-state charge density in the presence of the projectile. If, for example, the higher π^* resonance mixes strongly with a core-excited resonance built on a low-lying triplet state, the effect of such mixing on the resonance position would not be accounted for by our choice of configurations.

The many-electron description of polarisation through virtual excitations of the target molecule allows the SMC method [22, 23] to include the terms necessary to describe such resonant channel coupling along with terms describing "traditional" polarisation, that is, the relaxation of the electronic target density in the presence of the incident electron. As a test case for future studies of the DNA bases, we chose pyrazine, a close analogue of the pyrimidine bases, because of its high symmetry and the available experimental data on the positions of its three low-energy resonances. Detailed calculations [29, 30] reveal that the first two are nearly pure single-channel shape resonances, but the third is indeed, as long suspected [31], heavily mixed with core-excited resonances built on low-lying triplet states. Nenner and Schulz [31], in fact, posited that the higher-lying shape resonances they had observed in benzene and azabenzenes were probably mixed with core-excited shape resonances associated with low-lying excited states of the neutral molecule. Though the reality of such mixing was confirmed by subsequent observation of the decay of the 4.8 eV π^* resonance of benzene into electronically excited states [32] and is routinely invoked in discussions of experimental results [33], such mixing had not been previously accounted for in calculations on elastic electron-molecule collisions. Analogous channel coupling can be expected to occur in the nucleobases of DNA and RNA, and the failure of previous calculations [18, 19, 20] to allow for excitation to low-lying triplet states may account for much of the disagreement between the results of those calculations and related measurements [8, 12]. Future calculations for such π-ring systems using all-electron methods should take this resonant channel coupling into account, either by inclusion of the appropriate

configurations in the closed-channel expansion, or by explicitly including the lowest triplet states as open channels above their thresholds. On the other hand, it is less clear how such an effect, with its differential energy shifts among the π^* resonances, can be incorporated in single-particle models that treat polarisation as a local potential.

Mixed resonances decay not only into the electronically elastic channel but also into triplet states, and their presence in nucleobases suggests that at energies above 4 eV they may play a role in promoting DNA damage by slow electrons. Evidence suggests that ultraviolet photolysis of the nucleobases is in part suppressed by conical intersections that rapidly return singlet excited states to high vibrational levels of the ground state [34, 35] whose excess energy can be dissipated thermally. It is less clear, however, how well evolution may have provided against electron-induced damage where triplet states are involved. In fact, triplet states are thought to play a role in the formation of cyclobutyl pyrimidine dimer lesions in DNA [36], and it is possible to speculate that the observed increase in DNA single-strand breaks at electron collision energies above 4 eV [2, 4] may be promoted by the π^* resonances of thymine and cytosine at 4.05 and 4.5 eV, respectively [8, 12].

To make a closer connection between our results for the isolated bases and DNA itself, we have also studied electron scattering by the purine and pyrimidine nucleosides [18, 19] and by the nucleotide dAMP. For these larger systems, well-converged calculations including polarisation effects are not yet feasible with present versions of our computer codes, and we have treated them at the static–exchange level. Static-exchange calculations are fairly reliable at collision energies above 10 eV, where polarisation effects are small, and provide upper bounds to resonance positions even at lower energies. Moreover, by carrying out both static–exchange and static–exchange plus polarisation calculations on smaller, related molecules, and assuming that these results carry over to the larger systems, we can make informed estimates of the effects of polarisation in the larger molecules.

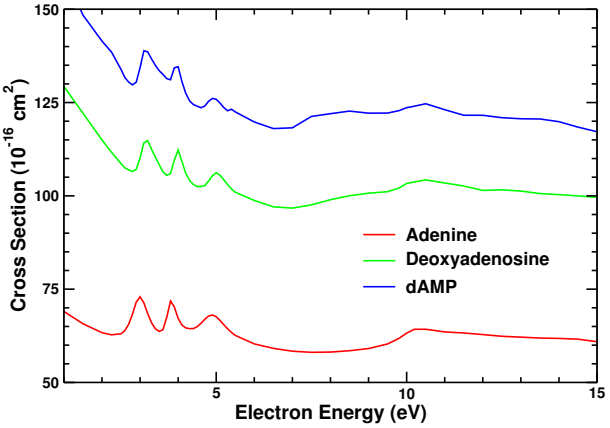

Figure 4. Integral elastic cross sections for electron scattering by adenine (bottom, red), 2-deoxyadenosine (middle, green), and 2-deoxyadenosine 5-monophosphate (top, blue), computed in the static–exchange approximation.

In Fig. 4 we compare the calculated integral elastic cross sections for adenine, its nucleoside dA, and its nucleotide dAMP. Details of the calculations, including the assumed nuclear geometries, are given in [18]. Because of the lack of symmetry in these molecules, we can no longer separate the π^* resonances cleanly from the background, as in adenine, but the resonance positions are still clearly visible in the total cross sections. There are small but systematic shifts in the resonance position between adenine and its nucleoside. Specifically, the three lowest

π^* resonances in dA lie at about 3.2, 4.0, and 5.0 eV or about 0.1–0.2 eV higher than their positions in adenine (Fig. 2). Imposition of planar geometry on the amino group of adenine, an approximation not made in the calculations on dA, may shift the π^* resonances upward, so the actual change in going from adenine to dA may be slightly larger than 0.1 to 0.2 eV. On the other hand, the π^* resonance positions virtually do not change going from dA to dAMP. Of course, there are other environmental effects on the π^* resonance positions in DNA, such as those that may arise from base pairing and solvation. We intend to explore such effects in future studies.

4. Summary

We have reported on some results of our high-level computational studies of low-energy electron collisions with the backbone constituents [21] and nucleobases of DNA and with the RNA base uracil [18, 19, 20], as well as with the nucleosides and nucleotides of the DNA bases [18, 19]. An emphasis of these studies has been the characterisation of the π^* resonances in the nucleobases, and our calculated positions for these resonances are in fact consistent with the assignments proposed by Burrow and coworkers [8, 12]. The discrepancy between the measured and calculated positions for the highest resonance in the bases is, however, consistently larger than for the two lowest-energy π^* resonances. While exploring this difference in the high-symmetry compound pyrazine, an analogue of the pyrimidine bases, we uncovered that the third π^* resonance has mixed character: It is partly an elastic-channel shape resonance and partly a core-excited resonance built on the low-lying triplet excited states, and the correct resonance energy can only be obtained by including such continuum mixing [29]. This result raises the interesting possibility that the higher π^* resonances may promote dissociation of DNA by providing doorways to triplet excited states.

Acknowledgments

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